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| NEWS 3 | JAN 25 | Annual Reload of MEDLINE database |
| NEWS 4 | FEB 16 | STN Express Maintenance Release, Version 8.4.2, Is Now Available for Download |
| NEWS 5 | FEB 16 | Derwent World Patents Index (DWPI) Revises Indexing of Author Abstracts |
| NEWS 6 | FEB 16 | New FASTA Display Formats Added to USGENE and PCTGEN |
| NEWS 7 | FEB 16 | INPADOCDB and INPAFAMDB Enriched with New Content and Features |
| NEWS 8 | FEB 16 | INSPEC Adding Its Own IPC codes and Author's E-mail Addresses |
| NEWS 9 | APR 02 | CAS Registry Number Crossover Limits Increased to 500,000 in Key STN Databases |
| NEWS 10 | APR 02 | PATDPAFULL: Application and priority number formats enhanced |
| NEWS 11 | APR 02 | DWPI: New display format ALLSTR available |
| NEWS 12 | APR 02 | New Thesaurus Added to Derwent Databases for Smooth Sailing through U.S. Patent Codes |
| NEWS 13 | APR 02 | EMBASE Adds Unique Records from MEDLINE, Expanding Coverage back to 1948 |
| NEWS 14 | APR 07 | CA/CAplus CLASS Display Streamlined with Removal of Pre-IPC 8 Data Fields |
| NEWS 15 | APR 07 | 50,000 World Traditional Medicine (WTM) Patents Now Available in CAplus |
| NEWS 16 | APR 07 | MEDLINE Coverage Is Extended Back to 1947 |

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=> FIL REGISTRY
COST IN U.S. DOLLARS

| | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.22 | 0.22 |

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STRUCTURE FILE UPDATES: 13 JUN 2010 HIGHEST RN 1227570-00-4
DICTIONARY FILE UPDATES: 13 JUN 2010 HIGHEST RN 1227570-00-4

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http://www.cas.org/support/stngen/stndoc/properties.html

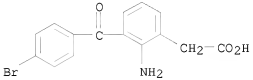
=> s 91714-92-2/rn
L1 0 91714-92-2/RN

=> s 91714-94-2/rn
L2 1 91714-94-2/RN

=> d 12

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2010 ACS on STN
RN **91714-94-2** REGISTRY
ED Entered STN: 16 Nov 1984
CN Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)- (CA INDEX NAME)
OTHER NAMES:
CN AHR 10282
CN Bromfenac
CN Xibrom

CN [2-Amino-3-(p-bromobenzoyl)phenyl]acetic acid
MF C15 H12 Br N O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

227 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
230 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s tyloxapol/cn
L3 1 TYLOXAPOL/CN

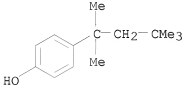
=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2010 ACS on STN
RN 25301-02-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethylene oxide, polymer with formaldehyde and p-(1,1,3,3-tetramethylbutyl)phenol (8CI)
CN Oxirane, polymer with formaldehyde and 4-(1,1,3,3-tetramethylbutyl)phenol (9CI)
CN Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane (9CI)
CN Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde (8CI)
OTHER NAMES:
CN Alevaire
CN Ethylene oxide-formaldehyde-4-(1,1,3,3-tetramethylbutyl)phenol copolymer
CN Ethylene oxide-formaldehyde-p-octylphenol copolymer
CN NSC 90255
CN Oxyethylated tertiary octyl-phenol-formaldehyde polymer
CN p-Isooctylpolyoxyethylenephenol formaldehyde polymer
CN Superinone
CN Triton A 20

CN Triton WR 1339
CN **Tyloxapol**
DR 9014-50-0, 9014-66-8, 9015-10-5
MF (C14 H22 O . C2 H4 O . C H2 O)x
CI PMS, COM
PCT Phenolic resin, Polyether, Polyether formed
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK*, PATDPASPC, PROMT, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 140-66-9
CMF C14 H22 O




CM 2

CRN 75-21-8
CMF C2 H4 O


CM 3

CRN 50-00-0
CMF C H2 O




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

844 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

844 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=> file medicine
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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     10.68      10.90

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FILE 'TOXCENTER' ENTERED AT 16:01:31 ON 14 JUN 2010


FILE 'USGENE' ENTERED AT 16:01:31 ON 14 JUN 2010


FILE 'USPATFULL' ENTERED AT 16:01:31 ON 14 JUN 2010


FILE 'USPATOLD' ENTERED AT 16:01:31 ON 14 JUN 2010

FILE 'USPAT2' ENTERED AT 16:01:31 ON 14 JUN 2010


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=> s l1 and l2
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'RN' IS NOT A VALID FIELD CODE
L4           0 L1 AND L2

=> s bromfenac and tyloxapol
L5         150 BROMFENAC AND TYLOXAPOL

=> s ophthalmic
L6      263335 OPHTHALMIC

=> s l5 and l6
L7         111 L5 AND L6

=> dup rem
ENTER L# LIST OR (END):l7
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2,
IMSPRODUCT, KOSMET, PCTGEN, USGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L7
L8          106 DUP REM L7 (5 DUPLICATES REMOVED)

=> s l8 and pd<2004
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'2004' NOT A VALID FIELD CODE
'2004' NOT A VALID FIELD CODE
  15 FILES SEARCHED...
'2004' NOT A VALID FIELD CODE
  22 FILES SEARCHED...
'2004' NOT A VALID FIELD CODE
  27 FILES SEARCHED...
  29 FILES SEARCHED...
L9           38 L8 AND PD<2004

=> s bromfenac sodium or bromfenac monosodium
L10        496 BROMFENAC SODIUM OR BROMFENAC MONOSODIUM
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=> s tyloxapol or alevaire or superinone or triton A 20 or triton WR 1339
   5 FILES SEARCHED...
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DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
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  25 FILES SEARCHED...
  30 FILES SEARCHED...
  31 FILES SEARCHED...
L11       9953 TYLOXAPOL OR ALEVAIRE OR SUPERINONE OR TRITON A 20 OR TRITON WR
               1339

=>

=> s l10 and l11
   5 FILES SEARCHED...
L12          8 L10 AND L11

=> dup rem
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PROCESSING COMPLETED FOR L12
L13           5 DUP REM L12 (3 DUPLICATES REMOVED)

=> d l13 1-5 ibib, kwic

L13  ANSWER 1 OF 5  USPATFULL on STN
ACCESSION NUMBER:       2008:362814  USPATFULL
TITLE:                  Transdermal Drug Delivery Formulation
INVENTOR(S):            Singh, Jagat, Scarborough, CANADA
PATENT ASSIGNEE(S):     NUVO RESEARCH INC., MISSISSAUGA, CANADA (non-U.S.
                        corporation)

                             NUMBER       KIND    DATE
                        --------------- ------ --------
PATENT INFORMATION:     US 20080319092     A1   20081225
APPLICATION INFO.:      US 2006-3028       A1   20060804  (12)
                        WO 2006-CA1271          20060804
                                                20080728  PCT 371 date

                               NUMBER             DATE
                        -------------------     --------
PRIORITY INFORMATION:   US 2005-705498P         20050805 (60)
                        US 2006-771030P         20060208 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   KATTEN MUCHIN ROSENMAN LLP, (C/O PATENT ADMINISTRATOR),
                        2900 K STREET NW, SUITE 200, WASHINGTON, DC,
                        20007-5118, US
NUMBER OF CLAIMS:       2
```

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2115
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; **Bromfenac Sodium**; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Ciprefadol Succinate; Ciramadol; Ciramadol Hydrochloride; Clonixeril;. . .
DETD . . . Trioxsalen; Triptorelin Pamoate; Trolamine Polypeptide Oleate Condensate; Trombodipine; Trometarnol; Tromethamine; Tropine Ester; Trospectomycin; Trovafloxacin; Trovafloxacin Mesylate; Trovirdine; Tucaresol; Tulobuterol; Tylogenin; **Tyloxapol**; Undecoylium Chloride; Undecoylium Chloride Iodine Complex; Unoprostone Isopropyl; Urapidil; Urea, C-13; Urea, C-14; Uridine Triphosphate; Valaciclovir; Valdecoxib; Valganciclovir Hydrochloride; Valproate. . .

L13 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2007:1421955 CAPLUS
DOCUMENT NUMBER: 148:39746
TITLE: Bromfenac ophthalmic formulations and methods of use
INVENTOR(S): Sawa, Shirou; Fujita, Shuhei; Grillone, Lisa R.
PATENT ASSIGNEE(S): Ista Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 21pp., Cont.-in-part of U.S. Ser. No. 525,006.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 20070287749 | A1 | 20071213 | US 2007-755662 | | 20070530 |
| US 20050239895 | A1 | 20051027 | US 2005-525006 | | 20050328 |
| PRIORITY APPLN. INFO.: | | | JP 2003-12427 | A | 20030121 |
| | | | US 2005-525006 | A2 | 20050328 |
| | | | WO 2004-JP350 | W | 20040116 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB . . . 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacol. acceptable salt or a hydrate thereof, an alkyl aryl polyether alc. type polymer such as **tyloxapol**, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate. The present invention further discloses new bromfenac ophthalmic. . .
IT 25301-02-4, **Tyloxapol** 25322-68-3D, Polyethylene glycol, esters
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bromfenac ophthalmic formulations and methods of use)
IT 91714-93-1, **Bromfenac sodium** 91714-94-2, Bromfenac
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(bromfenac ophthalmic formulations and methods of use)

L13 ANSWER 3 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2007:308290 USPATFULL
TITLE: Penetration Enhancer Combinations for Transdermal Delivery
INVENTOR(S): Mitragotri, Samir, Goleta, CA, UNITED STATES
Karande, Pankaj S., Somerville, MA, UNITED STATES
Jain, Amit K., Redwood City, CA, UNITED STATES

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 20070269379 | A1 | 20071122 | |
| APPLICATION INFO.: | US 2004-560571 | A1 | 20040721 | (10) |
| | WO 2004-US23634 | | 20040721 | |
| | | | 20070202 | PCT 371 date |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2003-560717P | 20030723 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Rober Berliner, Berliner & Associated, 555 W. Fifth Street, 31st Floor, Los Angeles, CA, 90013, US
NUMBER OF CLAIMS: 52
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Page(s)
LINE COUNT: 4179
DETD . . . Aminobenzoate Sodium; Amidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; **Bromfenac Sodium**; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Ciprefadol Succinate; Ciramadol; Ciramadol Hydrochloride; Clonixeril;. . .
DETD . . . Trioxsalen; Triptorelin Pamoate; Trolamine Polypeptide Oleate Condensate; Trombodipine; Trometarnol; Tromethamine; Tropine Ester; Trospectomycin; Trovafloxacin; Trovafloxacin Mesylate; Trovirdine; Tucaresol; Tulobuterol; Tylogenin; **Tyloxapol**; Undecoylium Chloride; Undecoylium Chloride Iodine Complex; Unoprostone Isopropyl; Urapidil; Urea, C-13; Urea, C-14; Uridine Triphosphate; Valaciclovir; Valdecoxib; Valganciclovir Hydrochloride; Valproate. . . .

L13 ANSWER 4 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2007:95155 USPATFULL
TITLE: Aqueous solution preparation containing aminoglycoside antibiotic and bromfenac
INVENTOR(S): Sawa, Shirou, 366-1-105, MINAMIBEFU 4-CHOME, NISHI-KU, KOBE-SHI, HYOGO, JAPAN 651-2116

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 20070082857 | A1 | 20070412 |

APPLICATION INFO.: US 2004-578359 A1 20041112 (10)
WO 2004-JP16849 20041112
20060606 PCT 371 date

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | JP 2003-384646 | 20031114 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WENDEROTH, LIND & PONACK, L.L.P., 2033 K STREET N. W., SUITE 800, WASHINGTON, DC, 20006-1021, US
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 807
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The nonionic surfactant includes, for example, polyoxyethylene sorbitan fatty acid esters (e.g. polysorbate 20, polysorbate 60, polysorbate 80, etc.); **tyloxapol**; polyoxyl 40 monostearate; polyoxyethylene hydrogenated castor oil (e.g. polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (60) hydrogenated castor oil, etc.); poloxamer; and the like. Preferable examples of the nonionic surfactant are polysorbate 80, **tyloxapol** or polyoxyl 40 monostearate.

SUMM . . . polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); citric acid or its pharmacologically acceptable salt and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.); monoethanolamine or its pharmacologically acceptable salt and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); monoethanolamine or its pharmacologically acceptable salt and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.); N-methylglucamine or its pharmacologically acceptable salt and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); N-methylglucamine or its pharmacologically acceptable salt and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80; polyoxyl 40 monostearate, etc.); nicotinamide and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); nicotinamide and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.); a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.) and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.), or the. . .

SUMM . . . purified water or water for injections), and to this solution were added an aminoglycoside antibiotic (e.g. gentamicin sulfate, etc.) and **bromfenac sodium**. The mixture was dissolved and adjusted to a pH of about not less than 7.0, preferably to a pH of. . .

SUMM . . . solvent, thereby to prepare a solution. To the solution were added an aminoglycoside antibiotic (e.g. tobramycin, gentamicin sulfate, etc.) and **bromfenac sodium**, and the resulting solution was adjusted to a pH of about not less than 7.0, preferably 7.5 to 8.5.

SUMM . . . above, thereby to prepare a solution. To the solution were added an aminoglycoside antibiotic (e.g. tobramycin, gentamicin sulfate,

etc.) and **bromfenac sodium**, and the resulting solution was adjutsted to a pH of about not less than 6.0, preferably 7.5 to 8.5.

SUMM . . . example, blepharitis, hordeolum, conjunctivitis, keratitis, dacryocystitis, etc. The dose in the case where an eye drop comprising 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate is applied may be 1 to 2 drops. . .

SUMM In the case where the aqueous solution preparation of the present invention comprising, for example, 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate is applied in the form of a nose. . .

SUMM In the case where the aqueous solution preparation of the present invention comprising, for example, 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate is applied in the form of an ear. . .

SUMM . . . various infectious diseases by the aqueous solution preparation of the present invention, an injection comprising, for example, 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate may be applied intramuscularly or subcutaneously in an. . .

DETD . . . 1 was prepared by dissolving boric acid and borax in a fixed amount of purified water and adding tobramycin and **bromfenac sodium** to the solution, followed by dissolution. With respect to the formulation 2, sodium citrate was further added to the formulation. . . was prepared by dissolving boric acid and borax in a fixed amount of purified water and adding gentamicin sulfate and **bromfenac sodium** thereto to make a solution. Then, the pH values of these formulations were adjusted by addition of hydrochloric acid and. . .

DETD A combination solution comprising tobramycin and **bromfenac sodium** as shown in Table 3 was prepared (formulation 4). Boric acid and borax were added to and dissolved in a fixed amount of purified water, and to this solution were added tobramycin and **bromfenac sodium**, followed by dissolution. Separately, each additive was added to and dissolved in the prescribed amount of purified water to give. . . determined according to the criteria as described in Example 1.

TABLE 3

Formulation of combination solution

| Component | Formulation 4 w/v % |
|---|---|
| **Bromfenac sodium** | 0.2 |
| Tobramycin | 0.6 |
| Boric acid | 1.14 |
| Borax | 4.5 |
| Hydrochloric acid | q.s. |
| Sodium hydroxide | q.s. |
| Purified water | q.s. |
| DETD . . . sorbate | 0.4 |
| Sodium glutamate | 0.6 |
| N-Methyl-2-pyrrolidone | 2.0 |

| | | |
|---|---|---|
| | Povidone K-30 | 4.0 |
| | Sodium alginate | 0.2 |
| | Sodium chondroitin sulfate | 2.0 |
| | Polysorbate 80 | 0.6 |
| | **Tyloxapol** | 0.6 |
| | Polyoxyl 40 monostearate | 0.6 |
| | Benzalkonium chloride | 0.2 |
| | Sodium lauryl sulfate | 0.2 |
| DETD | . . . alginate | 0.1 w/v % strongly turbid |
| | Sodium chondroitin sulfate | 1.0 w/v % strongly turbid |
| | Polysorbate 80 | 0.3 w/v % clear |
| | **Tyloxapol** | 0.3 w/v % clear |
| | Polyoxyl 40 monostearate | 0.3 w/v % clear |
| | Benzalkonium chloride | 0.1 w/v % strongly turbid |
| | Sodium lauryl. . . | |

DETD . . . monoethanolamine and N-methylglucamine; nicotinamide; a nonionic water-soluble polymer such as povidone K-30; or a nonionic surfactant such as polysorbate 80, **tyloxapol**, and polyoxyl 40 monostearate.

DETD Combination solutions comprising gentamicin sulfate and **bromfenac sodium** as shown in Table 6 were prepared (formulations 5 and 6). The formulation 5 was prepared by adding sodium dihydrogen phosphate and concentrated glycerine to a fixed amount of purified water, dissolving the mixture, and adding gentamicin sulfate and **bromfenac sodium** thereto, followed by dissolution. With respect to the formulation 6, boric acid and borax was added to and dissolved in a fixed amount of purified water, and to this solution were added gentamicin sulfate and **bromfenac sodium**, and then the mixture was dissolved. Separately, each additive solution was prepared as shown in Table 7. Each additive was. . . to the criteria as described in Example 1.

TABLE 6

| Component | Formulation of combination solution (w/v %) Formulation 5 | Formulation 6 |
|---|---|---|
| **Bromfenac sodium** | 0.2 | 0.2 |
| Gentamicin sulfate | 0.6 | 0.6 |
| Boric acid | -- | 1.14 |
| Borax | -- | 4.5 |
| Sodium dihydrogen phosphate | 0.2 | -- |
| Concentrated glycerine | 5.2 | -- |
| Hydrochloric acid | q.s. | q.s. |
| Sodium. . . | | |
| DETD . . . 2.0 | | |
| Nicotinamide | 2.0 | |
| Potassium sorbate | 0.4 | |
| Povidone K-30 | 4.0 | |
| Polyvinyl alcohol | 2.0 | |

| | | | | | |
|---|---|---|---|---|---|
| α-Cyclodextrin | 4.0 | | | | |
| Sodium alginate | | 0.2 | | | |
| Polysorbate 80 | | 0.6 | | | |
| **Tyloxapol** | | 0.6 | | | |
| Polyoxyl 40 monostearate | | 0.6 | | | |
| Benzalkonium chloride | | 0.2 | | | |
| Sodium lauryl sulfate | | 0.2 | | | |

DETD . . . 6.0 Clear

| | | | | |
|---|---|---|---|---|
| Sodium alginate | 0.1 | Formulation 6 | 6.5 | Strongly turbid |
| Polysorbate 80 | 0.3 | Formulation 6 | 6.5 | Clear |
| Polysorbate 80 | 0.3 | Formulation 6 | 6.0 | Clear |
| **Tyloxapol** | 0.3 | Formulation 6 | 6.5 | Clear |
| Polyoxyl 40 monostearate | 0.3 | Formulation 6 | 6.5 | Clear |
| Benzalkonium chloride | 0.1 | Formulation 6 | 6.5 | Strongly turbid |
| Sodium lauryl | 0.1 | Formulation. . . | | |

DETD . . . nicotinamide; a nonionic water-soluble polymer such as povidone, polyvinyl alcohol, and α-cyclodextrin; or a nonionic surfactant such as polysorbate 80, **tyloxapol**, and polyoxyl 40 monostearate. Furthermore, when α-cyclodextrin as a nonionic water-soluble polymer, or polysorbate 80 as a nonionic surfactant was. . .

DETD

TABLE 9

| | | |
|---|---|---|
| **Bromfenac sodium** 3/2 hydrate | 0.1 | g |
| Tobramycin | 0.3 | g |
| Boric acid | 1.4 | g |
| Borax | 0.8 | g |
| Hydrochloric acid | q.s. | |
| Purified water | q.s. | |

. . .

DETD Borax was dissolved in about 80 ml of purified water. Tobramycin and **bromfenac sodium** were added to the solution, and the mixture was dissolved. To the solution was added boric acid, and the mixture. . .

DETD

TABLE 10

| | | |
|---|---|---|
| **Bromfenac sodium** 3/2 hydrate | 0.1 | g |
| Tobramycin | 0.3 | g |
| Boric acid | 1.8 | g |
| Sodium citrate | 0.3 | g |
| Sodium hydroxide | q.s. | |
| Purified water. . . | | |

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added sodium citrate and. . .

DETD

TABLE 11

| | | |
|---|---|---|
| **Bromfenac sodium** 3/2 hydrate | 0.1 | g |
| Gentamicin sulfate | 0.3 | g |
| Polysorbate 80 | 0.3 | g |
| Sodium dihydrogen phosphate | 0.1 | g |
| Concentrated glycerine | 2.6. . . | |

DETD . . . were added to and dissolved in about 80 ml of purified water. To the solution were added gentamicin sulfate and **bromfenac sodium**, and the mixture was dissolved. Sodium hydroxide was added to the solution to adjust the pH, and purified water was. . .

DETD

TABLE 12

| | | |
|---|---|---|
| **Bromfenac sodium** 3/2 hydrate | 0.1 | g |
| Tobramycin | 0.3 | g |
| Boric acid | 1.6 | g |
| Povidone K-30 | 2.0 | g |
| Sodium hydroxide | q.s. | |
| Purified water. . . | | |

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added povidone K-30 and. . .

DETD

TABLE 13

| | | |
|---|---|---|
| **Bromfenac sodium** 3/2 hydrate | 0.1 | g |
| Tobramycin | 0.3 | g |
| Boric acid | 1.6 | g |
| N-Methylglucamine | 1.0 | g |
| Sodium hydroxide | q.s. | |
| Purified water | q.s. | |

. . .

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added N-methylglucamine and boric. . .

DETD

TABLE 14

| | | |
|---|---|---|
| **Bromfenac sodium** 3/2 hydrate | 0.1 | g |
| Tobramycin | 0.3 | g |
| Boric acid | 1.6 | g |
| Borax | 0.6 | g |
| Povidone K-30 | 1.0 | g |
| N-Methylglucamine | 0.1. . . | |

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added povidone K-30, N-methylglucamine,. . .

DETD

TABLE 15

| | | |
|---|---|---|
| **Bromfenac sodium** 3/2 hydrate | 0.1 | g |
| Tobramycin | 0.3 | g |
| Boric acid | 1.6 | g |
| Borax | 0.7 | g |
| Benzalkonium chloride | 0.005 | g |
| **Tyloxapol** | 0.02 | g |
| Povidone K-30 | 1.0 | g |
| Sodium edetate | 0.02 | g |
| Sodium hydroxide | q.s. | |
| Purified water | q.s. | |
| Total volume | 100 | ml |

. . .

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added **tyloxapol**, povidone K-30, sodium edetate, benzalkonium chloride, boric acid and borax, and the mixture was dissolved. The pH of the solution. . .

DETD . . . it is possible to obtain a clear aqueous solution preparation comprising an aminoglycoside antibiotic or its pharmacologically acceptable salt and **bromfenac sodium** or its pharmacologically acceptable salt.

IT 68-04-2, Sodium citrate 77-92-9, Citric acid, biological studies 98-92-0, Nicotinic acid amide 141-43-5, Monoethanolamine, biological studies 1403-66-3, Gentamicin 1405-41-0, Gentamicin sulfate 6284-40-8, N-Methylglucamine 32986-56-4, Tobramycin 91714-93-1, **Bromfenac sodium** 91714-94-2
(aqueous solns. containing aminoglycoside antibiotic and bromfenac)

L13 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 2

| | |
|---|---|
| ACCESSION NUMBER: | 2006:439980 CAPLUS |
| DOCUMENT NUMBER: | 144:440131 |
| TITLE: | Aqueous eye drops with accelerated intraocular migration |
| INVENTOR(S): | Sawa, Shirou; Fujimoto, Tomoko |
| PATENT ASSIGNEE(S): | Senju Pharmaceutical Co., Ltd., Japan |
| SOURCE: | PCT Int. Appl., 40 pp.<br>CODEN: PIXXD2 |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | Japanese |
| FAMILY ACC. NUM. COUNT: | 1 |
| PATENT INFORMATION: | |

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006049250 | A1 | 20060511 | WO 2005-JP20302 | 20051104 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,

IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| CA 2560559 | A1 | 20060511 | CA 2005-2560559 | 20051104 |
| CN 1993118 | A | 20070704 | CN 2005-80025963 | 20051104 |
| EP 1808170 | A1 | 20070718 | EP 2005-805529 | 20051104 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR | | | | |
| US 20070021507 | A1 | 20070125 | US 2006-568418 | 20060426 |
| IN 2006KN02763 | A | 20070601 | IN 2006-KN2763 | 20060921 |
| MX 2007001172 | A | 20070312 | MX 2007-1172 | 20070129 |
| PRIORITY APPLN. INFO.: | | | JP 2004-322569 A | 20041105 |
| | | | WO 2005-JP20302 W | 20051104 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB . . . inflammatory diseases on the external segment or anterior segment of the eye. For example, an aqueous eye drop solution contained **bromfenac sodium** hydrate 0.1, aminoethylsulfonic acid 0.5, benzalkonium chloride 0.005, **tyloxapol** 0.02, povidone 2, sodium edetate 0.02, boric acid 1.3, borax 0.74, NaOH q.s., and distilled water balance to 100 %.

=> d his

(FILE 'HOME' ENTERED AT 15:59:56 ON 14 JUN 2010)

FILE 'REGISTRY' ENTERED AT 16:00:17 ON 14 JUN 2010
L1 0 S 91714-92-2/RN
L2 1 S 91714-94-2/RN
L3 1 S TYLOXAPOL/CN

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CAPLUS, DDFB, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IMSDRUGNEWS, IMSPRODUCT, IPA, KOSMET, LIFESCI, MEDLINE, NAPRALERT, NLDB, PASCAL, PCTGEN, SCISEARCH, TOXCENTER, ...' ENTERED AT 16:01:31 ON 14 JUN 2010
L4 0 S L1 AND L2
L5 150 S BROMFENAC AND TYLOXAPOL
L6 263335 S OPHTHALMIC
L7 111 S L5 AND L6
L8 106 DUP REM L7 (5 DUPLICATES REMOVED)
L9 38 S L8 AND PD<2004
L10 496 S BROMFENAC SODIUM OR BROMFENAC MONOSODIUM
L11 9953 S TYLOXAPOL OR ALEVAIRE OR SUPERINONE OR TRITON A 20 OR TRITON
L12 8 S L10 AND L11
L13 5 DUP REM L12 (3 DUPLICATES REMOVED)

=> d l9 30-38 ibib, kwic

L9 ANSWER 30 OF 38 USPATFULL on STN
ACCESSION NUMBER: 1999:160081 USPATFULL

| | |
|---|---|
| TITLE: | Esters of non-steroidal anti-flammatory carboxylic acids |
| INVENTOR(S): | Hellberg, Mark, Arlington, TX, United States<br>Delgado, Pete, Fort Worth, TX, United States<br>Nixon, Jon C., Mansfield, TX, United States |
| PATENT ASSIGNEE(S): | Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5998465 | | 19991207 | <-- |
| APPLICATION INFO.: | US 1998-139506 | | 19980825 (9) | |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1998-23385, filed on 13 Feb 1998 which is a division of Ser. No. US 1995-526913, filed on 12 Sep 1995, now patented, Pat. No. US 5750564 | | | |
| DOCUMENT TYPE: | Utility | | | |
| FILE SEGMENT: | Granted | | | |
| PRIMARY EXAMINER: | Mach, D. Margaret | | | |
| LEGAL REPRESENTATIVE: | Mayo, Michael C. | | | |
| NUMBER OF CLAIMS: | 30 | | | |
| EXEMPLARY CLAIM: | 1 | | | |
| LINE COUNT: | 786 | | | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . using the compounds and compositions of the present invention to prevent and treat inflammatory disorders including ocular inflammation associated with **ophthalmic** disease and **ophthalmic** surgery.

SUMM . . . acid

| | | indoprofen |
|---|---|---|
| pirprofen | clidanac | fenoprofen |
| naproxen | fenclorac | meclofenamate |
| benoxaprofen | carprofen | isofezolac |
| aceloferac | fenbufen | etodolic acid |
| fleclozic acid | amfenac | efenamic acid |
| **bromfenac** | ketoprofen | fencloenac |
| alcofenac | orpanoxin | zomopirac |
| diflunisal | pranoprofen | zaltoprofen |

---

DETD The present invention is particularly directed to the provision of compositions adapted for treatment of **ophthalmic** tissues. The **ophthalmic** compositions of the present invention will include one or more compounds of formulas (I) and (II) and a pharmaceutically acceptable. . . semi-solid compositions. Suspensions may be preferred for compounds of formulas (I) and (II) which are relatively insoluble in water. The **ophthalmic** compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

DETD **Ophthalmic** products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include:. . .

DETD . . . the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the **ophthalmic** formulation. Such viscosity building agents

include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose,. . .

DETD As indicated above, use of the compounds of formulas (I)and (II) to prevent or reduce damage to **ophthalmic** tissues at the cellular level is a particularly important aspect of the present invention. **Ophthalmic** conditions which may be treated include, but are not limited to, cataracts, retinopathies, heredodegenerative diseases, macular degeneration, ocular ischemia, glaucoma, and damage associated with injuries to **ophthalmic** tissues, such as ischemia reperfusion injuries, photochemical injuries, and injuries associated with ocular surgery, particularly injuries to the retina, cornea. . . other tissues caused by exposure to light or surgical instruments. The compounds may also be used as an adjunct to **ophthalmic** surgery, such as by vitreal or subconjunctival injection following **ophthalmic** surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive **ophthalmic** procedures, or other types of surgery.

DETD Topical **ophthalmic** compositions useful for treating inflammation and/or tissue oxidative damage:

DETD

| Component | % w/v |
|---|---|
| Compound | 0.05-5.0 |
| **Tyloxapol** | 0.01-0.05 |
| HPMC | 0.5 |
| Benzalkonium Chloride | 0.01 |
| Sodium Chloride | 0.8 |
| Edetate Disodium | 0.01 |
| NaOH/HCl | q.s. pH 7.4 |
| Purified Water | q.s. 100. . . |

DETD A preferred topical **ophthalmic** composition useful for treating inflammation and/or tissue oxidative damage:

DETD

| Component | % w/v |
|---|---|
| Compound E | 0.10 |
| **Tyloxapol** | 0.01-0.05 |
| HPMC | 0.5 |
| Benzalkonium Chloride | 0.01 |
| Sodium Chloride | 0.8 |
| Edetate Disodium | 0.01 |
| NaOH/HCl | q.s. pH 7.4 |
| Purified Water | q.s. 100. . . |

DETD . . . either dry heat or filtered. The sterilized anti-inflammatory agent is weighed aseptically and placed into a pressurized ballmill container. The **tyloxapol**, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the. . .

CLM What is claimed:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac;

aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

24. The method according to claim 23, wherein the composition is administered to prevent or alleviate damage to **ophthalmic** tissues.

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

IT Drug delivery systems

(**ophthalmic**; preparation of esters of non-steroidal antiinflammatory agents with antioxidant activity)

L9 ANSWER 31 OF 38 USPATFULL on STN

| | |
|---|---|
| ACCESSION NUMBER: | 1999:63322 USPATFULL |
| TITLE: | Anti-oxidant esters of non-steroidal anti-inflammatory agents |
| INVENTOR(S): | Hellberg, Mark, Arlington, TX, United States<br>Delgado, Pete, Fort Worth, TX, United States<br>Nixon, Jon C., Mansfield, TX, United States |
| PATENT ASSIGNEE(S): | Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5908849 | | 19990601 | <-- |
| APPLICATION INFO.: | US 1998-23385 | | 19980213 (9) | |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1995-526913, filed on 12 Sep 1995, now patented, Pat. No. US 5750564 | | | |
| DOCUMENT TYPE: | Utility | | | |
| FILE SEGMENT: | Granted | | | |
| PRIMARY EXAMINER: | Rotman, Alan L. | | | |
| ASSISTANT EXAMINER: | Mach, Margaret M. | | | |
| LEGAL REPRESENTATIVE: | Mayo, Michael C. | | | |
| NUMBER OF CLAIMS: | 30 | | | |
| EXEMPLARY CLAIM: | 1 | | | |
| LINE COUNT: | 797 | | | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . using the compounds and compositions of the present invention to prevent and treat inflammatory disorders including ocular inflammation associated with **ophthalmic** disease and **ophthalmic** surgery.

SUMM

| | | |
|---|---|---|
| loxoprofen | tolfenamic acid | |
| | | indoprofen |
| pirprofen | clidanac | fenoprofen |
| naproxen | fenclorac | meclofenamate |
| benoxaprofen | carprofen | isofezolac |
| aceloferac | fenbufen | etodolic acid |
| fleclozic acid | | |
| | amfenac | efenamic acid |
| **bromfenac** | ketoprofen | fenclofenac |
| alcofenac | orpanoxin | zomopirac |
| diflunisal | pranoprofen | zaltoprofen |

DETD The present invention is particularly directed to the provision of compositions adapted for treatment of **ophthalmic** tissues. The **ophthalmic** compositions of the present invention will include one or more compounds of formulas (I) and (II) and a pharmaceutically acceptable. . . semi-solid compositions. Suspensions may be preferred for compounds of formulas (I) and (II) which are relatively insoluble in water. The **ophthalmic** compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

DETD **Ophthalmic** products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include:. . .

DETD . . . the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the **ophthalmic** formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose,. . .

DETD As indicated above, use of the compounds of formulas (I) and (II) to prevent or reduce damage to **ophthalmic** tissues at the cellular level is a particularly important aspect of the present invention. **Ophthalmic** conditions which may be treated include, but are not limited to, cataracts, retinopathies, heredodegenerative diseases, macular degeneration, ocular ischemia, glaucoma, and damage associated with injuries to **ophthalmic** tissues, such as ischemia reperfusion injuries, photochemical injuries, and injuries associated with ocular surgery, particularly injuries to the retina, cornea. . . other tissues caused by exposure to light or surgical instruments. The compounds may also be used as an adjunct to **ophthalmic** surgery, such as by vitreal or subconjunctival injection following **ophthalmic** surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive **ophthalmic** procedures, or other types of surgery.

DETD Topical **ophthalmic** compositions useful for treating inflammation and/or tissue oxidative damage:

DETD

| Component | % w/v |
|---|---|
| Compound | 0.05-5.0 |
| **Tyloxapol** | 0.01-0.05 |
| HPMC | 0.5 |
| Benzalkonium Chloride | 0.01 |
| Sodium Chloride | 0.8 |
| Edetate Disodium | 0.01 |
| NaOH/HCl | q.s. pH 7.4 |
| Purified Water | q.s. 100 mL |

DETD A preferred topical **ophthalmic** composition useful for treating inflammation and/or tissue oxidative damage:

DETD

| Component | % w/v |
|---|---|
| Compound E | 0.10 |
| **Tyloxapol** | 0.01-0.05 |
| HPMC | 0.5 |
| Benzalkonium Chloride | 0.01 |
| Sodium Chloride | 0.8 |
| Edetate Disodium | 0.01 |
| NaOH/HCl | q.s. pH 7.4 |
| Purified Water | q.s. 100 mL |

DETD . . . either dry heat or filtered. The sterilized anti-inflammatory agent is weighed aseptically and placed into a pressurized ballmill container. The **tyloxapol**, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

24. The method according to claim 23, wherein the composition is administered to prevent or alleviate damage to **ophthalmic** tissues.

CLM What is claimed:
. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .
IT Drug delivery systems
(**ophthalmic**; preparation of esters of non-steroidal antiinflammatory agents with antioxidant activity)

L9 ANSWER 32 OF 38 USPATFULL on STN

| | |
|---|---|
| ACCESSION NUMBER: | 1998:51640 USPATFULL |
| TITLE: | Anti-oxidant esters of non-steroidal anti-inflammatory agents |
| INVENTOR(S): | Hellberg, Mark, 52211 Overridge Dr., Arlington, TX, United States 76017<br>Delgado, Pete, 4315 N. Segura Ct., Fort Worth, TX, United States 76132<br>Nixon, Jon C., 1616 Hastings Dr., Mansfield, TX, United States 76132 |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5750564 | | 19980512 | <-- |
| APPLICATION INFO.: | US 1995-526913 | | 19950912 | (8) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | Granted |
| PRIMARY EXAMINER: | Richter, Johann |
| ASSISTANT EXAMINER: | Stockton, Laura L. |
| LEGAL REPRESENTATIVE: | Mayo, Michael C. |
| NUMBER OF CLAIMS: | 30 |
| EXEMPLARY CLAIM: | 1 |
| LINE COUNT: | 744 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . using the compounds and compositions of the present invention to prevent and treat inflammatory disorders including ocular inflammation associated with **ophthalmic** disease and **ophthalmic** surgery.

SUMM

| | | |
|---|---|---|
| loxoprofen | tolfenamic acid | |
| | | indoprofen |
| pirprofen | clidanac | fenoprofen |
| naproxen | fenclorac | meclofenamate |
| benoxaprofen | carprofen | isofezolac |
| aceloferac | fenbufen | etodolic acid |
| fleclozic acid | | |
| | amfenac | efenamic acid |
| **bromfenac** | ketoprofen | fenclofenac |
| alcofenac | orpanoxin | zomopirac |
| diflunisal | pranoprofen | zaltoprofen |

DETD The present invention is particularly directed to the provision of compositions adapted for treatment of **ophthalmic** tissues. The **ophthalmic** compositions of the present invention will include one or more compounds of formulas (I) and (II) and a pharmaceutically acceptable. . . semi-solid compositions. Suspensions may be preferred for compounds of formulas (I) and (II) which are relatively insoluble in water. The **ophthalmic** compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

DETD **Ophthalmic** products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include:. . .

DETD . . . the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the **ophthalmic** formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose,. . .

DETD As indicated above, use of the compounds of formulas (I) and (II) to prevent or reduce damage to **ophthalmic** tissues at the cellular level is a particularly important aspect of the present invention. **Ophthalmic** conditions which may be treated include, but are not limited to, cataracts, retinopathies, heredodegenerative diseases, macular degeneration, ocular ischemia, glaucoma, and damage associated with injuries to **ophthalmic** tissues, such as ischemia reperfusion injuries, photochemical injuries, and injuries associated with ocular surgery, particularly injuries to the retina, cornea. . . other tissues caused by exposure to light or surgical instruments. The compounds may also be used as an adjunct to **ophthalmic** surgery, such as by vitreal or subconjunctival injection following **ophthalmic** surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive **ophthalmic** procedures, or other types of surgery.

DETD Topical **ophthalmic** compositions useful for treating inflammation and/or tissue oxidative damage:

DETD

| Component | % w/v |
|---|---|
| Compound | 0.05-5.0 |
| **Tyloxapol** | 0.01-0.05 |
| HPMC | 0.5 |
| Benzalkonium Chloride | 0.01 |
| Sodium Chloride | 0.8 |
| Edetate Disodium | 0.01 |
| NaOH/HCl | q.s. pH 7.4 |
| Purified Water | q.s. 100 mL |

DETD A preferred topical **ophthalmic** composition useful for treating inflammation and/or tissue oxidative damage:

DETD

| Component | % w/v |
|---|---|

| | |
|---|---|
| Compound E | 0.10 |
| **Tyloxapol** | 0.01-0.05 |
| HPMC | 0.5 |
| Benzalkonium Chloride | 0.01 |
| Sodium Chloride | 0.8 |
| Edetate Disodium | 0.01 |
| NaOH/HCl | q.s. pH 7.4 |
| Purified Water | q.s. 100 mL |

DETD . . . either dry heat or filtered. The sterilized anti-inflammatory agent is weighed aseptically and placed into a pressurized ballmill container. The **tyloxapol**, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen, clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

24. The method according to claim 23, wherein the composition is administered to prevent or alleviate damage to **ophthalmic** tissues.

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid: fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

IT Drug delivery systems
(**ophthalmic**; preparation of esters of non-steroidal antiinflammatory agents with antioxidant activity)

L9 ANSWER 33 OF 38 USPATFULL on STN

ACCESSION NUMBER: 97:68150 USPATFULL

TITLE: Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds

INVENTOR(S): Desai, Suketu Dipakbhai, Fort Worth, TX, United States

PATENT ASSIGNEE(S): Nelms, Diane S., Fort Worth, TX, United States
Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5653972 | | 19970805 | <-- |
| APPLICATION INFO.: | US 1996-700960 | | 19960821 | (8) |

RELATED APPLN. INFO.: Division of Ser. No. US 1994-340763, filed on 16 Nov 1994
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Howard, Sharon
LEGAL REPRESENTATIVE: Ryan, Patrick M.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 309
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds

AB Disclosed are storage-stable preserved **ophthalmic** compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds and boric acid.

SUMM The present invention relates generally to **ophthalmic** compositions. In particular, the present invention relates to the use of a polymeric quaternary ammonium compound and boric acid to provide preserved, storage-stable **ophthalmic** compositions of acidic drugs.

SUMM **Ophthalmic** formulations generally contain one or more active compounds along with excipients such as surfactants, comforting agents, complexing agents, stabilizers, buffering systems, chelating agents, viscosity agents or gelling polymers and anti-oxidants. **Ophthalmic** formulations which are intended for multidose use require a preservative.

SUMM Organo-mercurials have been used as preservatives in **ophthalmic** formulations including **ophthalmic** solutions of acidic drugs. These organo-mercurials include thimerosal, phenylmercuric acetate and phenylmercuric nitrate. Organo-mercurials, however, have limitations due to potential. . .

SUMM Sorbic acid, has also been used to preserve **ophthalmic** formulations, but it too possesses poor chemical stability as well as poor antimicrobial activity.

SUMM Benzalkonium chloride is a widely used preservative in **ophthalmic** solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with **ophthalmic** compositions of drugs with acidic groups, such as nonsteroidal antiinflammatory drugs ("NSAIDS"). These preservative lose their ability to function as. . .

SUMM U.S. Pat. No. 5,110,493 discloses stable **ophthalmic** NSAID formulations which do not contain organo-mercurial preservatives. Instead, the reference NSAID formulations use quaternary ammonium compounds, such as cetyltrimethylammonium. . .

SUMM PCT application WO 94/15597 discloses the use of lauralkonium chloride, the C.sub.12 homolog of benzalkonium chloride, in **ophthalmic** formulations of drugs which are incompatible with benzalkonium chloride. Unlike the mixture of alkyldimethylbenzylammonium chloride known as benzalkonium chloride, this. . .

SUMM . . . safe, stable, and able to meet both the United States Pharmacopoeia (USP) and European Pharmacopoeia (Ph.Eur.) preservative effectiveness requirements for **ophthalmic** formulations of acidic drugs has forced pharmaceutical companies to develop more than one formulation of the same drug, with each. . .

SUMM U.S. Pat. No. 4,960,799 discloses storage stable aqueous **ophthalmic** compositions containing diclofenac, a nonsteroidal antiinflammatory drug, and/or its pharmaceutically acceptable salts. The reference compositions include EDTA as a stabilizing. . .

SUMM . . . None of these references disclose the use of a polymeric quaternary ammonium compound as a preservative in any formulations of **ophthalmic** drugs.

SUMM . . . discovered that the use of a combination of a polymeric quaternary ammonium compound such as Polyquad® and boric acid in **ophthalmic** compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of a polymeric quaternary ammonium compound and boric acid is useful in **ophthalmic** compositions of acidic drugs such as prostaglandins, antifungals, antibacterials, and diagnostic agents. This preservative combination is especially useful in **ophthalmic** solutions of drugs containing either a carboxyl group such as non-steroidal antiinflammatory drugs (NSAIDS) or a sulfonamide group such as. . .

SUMM Among other factors, the present invention is based on the discovery that **ophthalmic** compositions containing a polymeric quaternary ammonium compound and boric acid may be effectively preserved by the USP and Ph.Eur. preservative. . .

SUMM Suitable **ophthalmic** agents which may be included in the compositions of the present invention and administered via the method of the present. . . derivatives; non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl-alkanoic acids, such as diclofenac, **bromfenac**, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterials and anti-infectives, including sulfa drugs, such as sulfacetamide sodium, and beta-lactams such as penicillins and cephalosporins; and diagnostic agents such as sodium fluorescein. Combinations of **ophthalmic** agents may also be used in the compositions of the present invention.

SUMM . . . chlorobutanol, and biguanides such as chlorhexidine and hydroxypropyl methyl biguanide), surfactants (e.g. poloxamers such as Pluronics®; polysorbates such as Tweens®; **tyloxapol**; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®), and tonicity agents (e.g., sodium chloride, mannitol, dextrose and. . .

SUMM The **ophthalmic** compositions of the present invention may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical. . .

DETD . . . the formulation. The rate or level of antimicrobial activity determined compliance with the USP and/or Ph.Eur. preservative efficacy standards for **ophthalmic** preparations.

DETD The compendial preservative standards for **ophthalmic** preparations are presented below:

DETD . . . of the preservative challenge study conducted on Formulation A are shown below in Table 1. These results illustrate that an **ophthalmic** formulation of an acidic drug can be globally preserved, that is, can comply with the USP and Ph.Eur. A preservative effectiveness requirements for **ophthalmic** preparations, using a combination of a polymeric quaternary ammonium compound and boric acid.

CLM What is claimed is:

1. A method for treating or controlling ocular inflammation comprising the topical ocular application of a preserved storage stable **ophthalmic** composition comprising a therapeutically-effective amount of one or more acidic non-steroidal anti-inflammatory agents, a combination of an antimicrobial polymeric quaternary. . .

CLM What is claimed is:

5. The method of claim 2 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of **bromfenac** and its ophthalmically acceptable salts, esters, amides or prodrugs.

ST **ophthalmic** prepn quaternary ammonium polymer preservative; diclofenac borate Polyquad **ophthalmic** prepn

IT Inflammation inhibitors
(nonsteroidal; preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Biocides

IT Glaucoma (disease)
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Diagnosis
(agents, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Pharmaceutical dosage forms
(**ophthalmic**, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Quaternary ammonium compounds, biological studies
(polymers, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT 53-86-1, Indomethacin 5104-49-4, Flurbiprofen 10043-35-3, Boric acid, biological studies 10043-35-3D, Boric acid, polyol complexes 15307-79-6, Sodium diclofenac 15307-86-5, Diclofenac 22071-15-4, Ketoprofen 40828-46-4, Suprofen 74103-06-3, Ketorolac 75345-27-6, Polyquaternium-1 91714-94-2, **Bromfenac**
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

L9 ANSWER 34 OF 38 USPATFULL on STN

ACCESSION NUMBER: 97:14409 USPATFULL

TITLE: Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds

INVENTOR(S): Desai, Suketu D., Fort Worth, TX, United States
Nelms, Diane S., Fort Worth, TX, United States

PATENT ASSIGNEE(S): Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5603929 | | 19970218 | <-- |
| APPLICATION INFO.: | US 1994-340763 | | 19941116 | (8) |
| DOCUMENT TYPE: | Utility | | | |
| FILE SEGMENT: | Granted | | | |
| PRIMARY EXAMINER: | Page, Thurman K. | | | |
| ASSISTANT EXAMINER: | Howard, Sharon | | | |
| LEGAL REPRESENTATIVE: | Ryan, Patrick M. | | | |
| NUMBER OF CLAIMS: | 20 | | | |
| EXEMPLARY CLAIM: | 1 | | | |
| LINE COUNT: | 361 | | | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds

AB Disclosed are storage-stable preserved **ophthalmic** compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds and boric acid.

SUMM The present invention relates generally to **ophthalmic** compositions. In particular, the present invention relates to the use of a polymeric quaternary ammonium compound and boric acid to provide preserved, storage-stable **ophthalmic** compositions of acidic drugs.

SUMM **Ophthalmic** formulations generally contain one or more active compounds along with excipients such as surfactants, comforting agents, complexing agents, stabilizers, buffering systems, chelating agents, viscosity agents or gelling polymers and anti-oxidants. **Ophthalmic** formulations which are intended for multidose use require a preservative.

SUMM Organo-mercurials have been used as preservatives in **ophthalmic** formulations including **ophthalmic** solutions of acidic drugs. These organo-mercurials include thimerosal, phenylmercuric acetate and phenylmercuric nitrate. Organo-mercurials, however, have limitations due to potential. . .

SUMM Sorbic acid, has also been used to preserve **ophthalmic** formulations, but it too possesses poor chemical stability as well as poor antimicrobial activity.

SUMM Benzalkonium chloride is a widely used preservative in **ophthalmic** solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with **ophthalmic** compositions of drugs with acidic groups, such as nonsteroidal antiinflammatory drugs ("NSAIDS"). These preservative lose their ability to function as. . .

SUMM U.S. Pat. No. 5,110,493 discloses stable **ophthalmic** NSAID formulations which do not contain organo-mercurial preservatives. Instead, the reference NSAID formulations use quaternary ammonium compounds, such as cetyltrimethylammonium. . .

SUMM PCT application WO 94/15597 discloses the use of lauralkonium chloride, the C.sub.12 homolog of benzalkonium chloride, in **ophthalmic** formulations of drugs which are incompatible with benzalkonium chloride. Unlike the mixture of alkyldimethylbenzylammonium chloride known as benzalkonium chloride, this. . .

SUMM . . . stable, and able to meet both the United States Pharmacopoeia (USP) and European Pharmacopoeia (Ph. Eur.) preservative effectiveness requirements for **ophthalmic** formulations of acidic drugs has forced pharmaceutical companies to develop more than one formulation of the same drug, with each. . .

SUMM U.S. Pat. No. 4,960,799 discloses storage stable aqueous **ophthalmic** compositions containing diclofenac, a nonsteroidal antiinflammatory drug, and/or its pharmaceutically acceptable salts. The reference compositions include EDTA as a stabilizing. . .

SUMM . . . contact lens and artificial tear solutions, also discloses the use of certain polymeric quaternary ammonium compounds in formulations containing certain **ophthalmic** drugs. However, neither this reference nor any of the other references mentioned above discloses the use of a polymeric quaternary ammonium compound as a preservative in formulations of acidic **ophthalmic** drugs, that is, drugs which may be incompatible with positively charged preservatives.

SUMM . . . discovered that the use of a combination of a polymeric quaternary ammonium compound such as POLYQUAD® and boric acid in **ophthalmic** compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of a polymeric quaternary ammonium compound and boric acid is useful in **ophthalmic** compositions of acidic drugs such as prostaglandins, antifungals, antibactedals, and diagnostic agents. This preservative combination is especially useful in **ophthalmic** solutions of drugs containing either a carboxyl group such as non-steroidal anti-inflammatory drugs (NSAIDS) or a sulfonamide group such as. . .

SUMM Among other factors, the present invention is based on the discovery that **ophthalmic** compositions containing a polymeric quaternary ammonium compound and boric acid may be effectively preserved by the USP and Ph. Eur.. . .

DETD Suitable **ophthalmic** agents which may be included in the compositions of the present invention and administered via the method of the present. . . derivatives; non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl-alkanoic acids, such as diclofenac, **bromfenac**, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterials and anti-infectives, including sulfa drugs, such as sulfacetamide sodium, and beta-lactams such as penicillins and cephalosporins; and diagnostic agents such as sodium fluorescein. Combinations of **ophthalmic** agents may also be used in the compositions of the present invention.

DETD . . . chlorobutanol, and biguanides such as chlorhexidine and hydroxypropyl methyl biguanide), surfactants (e.g. poloxamers such as Pluronics®; polysorbates such as Tweens®; **tyloxapol**; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®), and tonicity agents (e.g., sodium chloride, mannitol, dextrose and. . .

DETD The **ophthalmic** compositions of the present invention may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical. . .

DETD . . . formulation. The rate or level of antimicrobial activity determined compliance with the USP and/or Ph. Eur. preservative efficacy standards for **ophthalmic** preparations.

DETD The compendial preservative standards for **ophthalmic**

preparations are presented below:

DETD . . . of the preservative challenge study conducted on Formulation A are shown below in Table 1. These results illustrate that an **ophthalmic** formulation of an acidic drug can be globally preserved, that is, can comply with the USP and Ph. Eur. A preservative effectiveness requirements for **ophthalmic** preparations, using a combination of a polymeric quaternary ammonium compound and boric acid.

CLM What is claimed is:
1. A storage stable **ophthalmic** composition comprising a therapeutically effective amount of one or more acidic **ophthalmic** agents, a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid in an amount effective to meet at. . . minimum United States Pharmacopeia XXII and European Pharmacopeia (1994) preservative effectiveness requirements, and an ophthalmically acceptable vehicle; wherein the acidic **ophthalmic** agent is selected from the group consisting of anti-glaucoma and non-steroidal anti-inflammatory agents; provided that the composition does not contain. . .

CLM What is claimed is:
2. The composition of claim 1 wherein the **ophthalmic** agent is a non-steroidal anti-inflammatory agent.

CLM What is claimed is:
. . . The composition of claim 3 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: diclofenac, flurbiprofen, suprofen, **bromfenac**, keterolac, indomethacin, ketaprofen, and ophthalmically acceptable salts, esters, amides or prodrugs thereof.

CLM What is claimed is:
7. The composition of claim 4 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of **bromfenac** and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

CLM What is claimed is:
19. An **ophthalmic** formulation comprising diclofenac or an ophthalmically acceptable salt, ester, amide or prodrug thereof, and a combination of an antimicrobial polymeric. . .

ST **ophthalmic** prepn quaternary ammonium polymer preservative; diclofenac borate Polyquad **ophthalmic** prepn

IT Inflammation inhibitors
(nonsteroidal; preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Biocides

IT Glaucoma (disease)
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Diagnosis
(agents, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Pharmaceutical dosage forms
(**ophthalmic**, preserved **ophthalmic** drug compns.

containing polymeric quaternary ammonium compds.)
IT Quaternary ammonium compounds, biological studies
(polymers, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)
IT 53-86-1, Indomethacin 5104-49-4, Flurbiprofen 10043-35-3, Boric acid, biological studies 10043-35-3D, Boric acid, polyol complexes 15307-79-6, Sodium diclofenac 15307-86-5, Diclofenac 22071-15-4, Ketoprofen 40828-46-4, Suprofen 74103-06-3, Ketorolac 75345-27-6, Polyquaternium-1 91714-94-2, **Bromfenac**
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

L9 ANSWER 35 OF 38 USPAT2 on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2004:334304 USPAT2 |
| TITLE: | Cyclooxygenase-2 inhibitor compositions having rapid onset of therapeutic effect |
| INVENTOR(S): | Kararli, Tugrul T., Skokie, IL, UNITED STATES<br>Kontny, Mark J., Libertyville, IL, UNITED STATES<br>Desai, Subhash, Wilmette, IL, UNITED STATES<br>Hageman, Michael J., Portage, MI, UNITED STATES<br>Haskell, Royal J., Kalamazoo, MI, UNITED STATES(4) |
| PATENT ASSIGNEE(S): | Pharmacia Corporation, St. Louis, MO, UNITED STATES (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 7172769 | B2 | 20070206 | |
| | WO 2001041760 | | 20010614 | <-- |
| APPLICATION INFO.: | US 2000-31898 | | 20001206 | (10) |
| | WO 2000-US32434 | | 20001206 | |
| | | | 20020730 | PCT 371 date |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1999-169856P | 19991209 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | GRANTED |
| PRIMARY EXAMINER: | Azpuru, Carlos A. |
| LEGAL REPRESENTATIVE: | Fitzsimmons, Patricia K., Ashbrook, Charles |
| NUMBER OF CLAIMS: | 17 |
| EXEMPLARY CLAIM: | 1,2 |
| NUMBER OF DRAWINGS: | 4 Drawing Figure(s); 3 Drawing Page(s) |
| LINE COUNT: | 1893 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following **ophthalmic** surgery such as cataract surgery or refractive surgery.
DETD Such compositions are useful in treatment of **ophthalmic** diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.
DETD . . . ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone,

bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitrarnide, α-bisabolol, **bromfenac**, ρ-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen,. . .

DETD . . . In this embodiment the surface modifying agent is a nonionic liquid polymer of the alkylaryl polyether alcohol type, for example **tyloxapol**. Optionally an additional surface modifying agent can be present.

DETD . . . of an oil, a selective COX-2 inhibitory drug in the presence of surface modifying agents (e.g., gelatin, casein, lecithin, polyvinylpyrrolidone, **tyloxapol**, poloxamers, other block polymers, etc.) substantially as disclosed in above-cited U.S. Pat. No. 5,560,931. In this embodiment, the drug particles. . .

DETD . . . comprising a first particle distribution of a selective COX-2 inhibitory drug together with a surface modifying agent such as polysulfated **tyloxapol** by a process comprising the steps of (a) placing the dispersion between a first electrode and a second electrode; and. . .

DETD . . . fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, **tyloxapol**, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to. . .

L9 ANSWER 36 OF 38 USPAT2 on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2004:307964 USPAT2 |
| TITLE: | Dual-release compositions of a cyclooxygenase-2 inhibitor |
| INVENTOR(S): | Desai, Subhash, Wilmette, IL, UNITED STATES<br>Nadkarni, Sreekant R., Gurnee, IL, UNITED STATES<br>Wald, Randy J., Portage, MI, UNITED STATES<br>DeBrincat, Gary A., Battle Creek, MI, UNITED STATES |
| PATENT ASSIGNEE(S): | Pharmacia Corporation (of Pfizer, Inc.), St Louis, MO, UNITED STATES (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 7220434 | B2 | 20070522 | |
| | WO 2001045706 | | 20010628 | <-- |
| APPLICATION INFO.: | US 2000-169039 | | 20001220 | (10) |
| | WO 2000-US34754 | | 20001220 | |
| | | | 20040223 | PCT 371 date |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | GRANTED |
| PRIMARY EXAMINER: | Hartley, Michael G. |
| ASSISTANT EXAMINER: | Ebrahim, Nabila |
| LEGAL REPRESENTATIVE: | Fitzsimmons, Patricia K., Ashbrook, Charles W. |
| NUMBER OF CLAIMS: | 18 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 1 Drawing Figure(s); 1 Drawing Page(s) |
| LINE COUNT: | 2151 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following **ophthalmic** surgery such as cataract surgery or refractive surgery.

DETD Such compositions are useful in treatment of **ophthalmic** diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

DETD . . . ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, **bromfenac**, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen,. . .

DETD . . . fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, **tyloxapol**, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to. . .

L9 ANSWER 37 OF 38 USPAT2 on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2002:48624 USPAT2 |
| TITLE: | Compositions and methods for treating **ophthalmic** and otic infections |
| INVENTOR(S): | Cagle, Gerald, Fort Worth, TX, United States<br>Abshire, Robert L., Fort Worth, TX, United States<br>Stroman, David W., Irving, TX, United States<br>McLean, Celeste H., Fort Worth, TX, United States<br>Clark, Linda L., Grandview, TX, United States<br>Yanni, John M., Burleson, TX, United States |
| PATENT ASSIGNEE(S): | Alcon Manufacturing, Ltd., Fort Worth, TX, United States (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6440964 | B2 | 20020827 | <-- |
| APPLICATION INFO.: | US 2001-887771 | | 20010622 (9) | |
| RELATED APPLN. INFO.: | Continuation-in-part of Ser. No. US 577262 | | | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1998-102504P | 19980930 (60) |
| | US 1998-102506P | 19980930 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | GRANTED |
| PRIMARY EXAMINER: | Fay, Zohreh |
| LEGAL REPRESENTATIVE: | Brown, Gregg C. |
| NUMBER OF CLAIMS: | 6 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 1 Drawing Figure(s); 1 Drawing Page(s) |
| LINE COUNT: | 510 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Compositions and methods for treating **ophthalmic** and otic infections

AB **Ophthalmic**, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat **ophthalmic**, otic and nasal conditions by topically applying the compositions to the affected tissues. The compositions and methods of the invention are particularly useful in the treatment of acute otitis externa infections and **ophthalmic** infections attributable to one or both of two newly identified Microbacterium species, Microbacterium otitidis and Microbacterium alconae.

SUMM The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of **ophthalmic**, otic and nasal infections, particularly bacterial infections, and to methods of treating **ophthalmic**, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are. . .

SUMM Quinolone antibiotics have been previously utilized to treat **ophthalmic** and otic infections. For example, a topical **ophthalmic** composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN.TM. (Ciprofloxacin 0.3%) **Ophthalmic** Solution, and a topical otic composition containing a combination of ciprofloxacin and hydrocortisone is marketed by Alcon Laboratories, Inc. under the name CIPRO.TM. HC. The following quinolones have also been utilized in **ophthalmic** antibiotic compositions:

SUMM The foregoing quinolone antibiotic compositions are generally effective in treating **ophthalmic** infections, and have distinct advantages over prior **ophthalmic** antibiotic compositions, particularly those having relatively limited spectrums of antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which. . . and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the **ophthalmic** quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key **ophthalmic** pathogens, and less prone to the development of resistance by those pathogens.

SUMM **Ophthalmic**, otic and nasal infections are frequently accompanied by inflammation of the infected **ophthalmic**, otic and nasal tissues and perhaps even surrounding tissues. Similarly, **ophthalmic**, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for **ophthalmic**, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of. . .

SUMM The invention is based on the use of a potent new class of antibiotics to treat **ophthalmic**, otic and nasal infections, as well as the use of these antibiotics prior to surgery to sterilize the surgical field and prophylactically following surgery or other trauma to

**ophthalmic**, otic or nasal tissues to minimize the risk of infection. The compositions of the present invention may also be administered to the affected tissues during **ophthalmic**, otic or nasal surgical procedures to prevent or alleviate post-surgical infection. As utilized herein, the terms "treat", "treating" and derivations. . .

SUMM The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation associated with infections of **ophthalmic**, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to **ophthalmic**, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to **ophthalmic**, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

SUMM Examples of **ophthalmic** conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various **ophthalmic** surgical procedures that create a risk of infection.

SUMM . . . that have been identified as being associated with acute otitis extema infections have also been discovered to be associated with **ophthalmic** infections. As indicated above, the antibiotics utilized in the present invention have a high level of antimicrobial activity against these newly discovered **ophthalmic** pathogens, and as a result, the compositions of the present invention are particularly useful in treating **ophthalmic** infections involving these species.

SUMM The compositions of the present invention are specially formulated for topical application to **ophthalmic**, otic and nasal tissues. The compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to **ophthalmic**, otic and nasal tissues, including tissues that have been compromised as the result of preexisting disease, trauma, surgery or other. . .

DETD . . . to as the "minimum bactericidal concentration" or "MBC". The minimum inhibitory concentration of Moxifloxacin for several bacteria commonly associated with **ophthalmic**, otic and nasal infections are provided in the following table:

DETD Microbacterium otitidis and Microbacterium alconae have also been discovered to be pathogens in infections of **ophthalmic** tissues, such as conjunctivitis and blepharitis. The compositions of the present invention are therefore particularly useful in treating **ophthalmic** infections involving one or both of these species.

DETD The appropriate antibiotic concentration for **ophthalmic** compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in. . . to or greater than the MIC.sub.90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with **ophthalmic** infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of. . .

DETD The preferred glucocorticoids for **ophthalmic** and otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, and hydrocortisone. The preferred glucocorticoids for nasal use include mometasone, fluticasone,. . .

DETD . . . described in U.S. Pat. No. 5,223,493 (Boltralik) are also preferred steroidal anti-inflammatory agents, particularly with respect to compositions for treating **ophthalmic** inflammation. The following compounds are especially preferred: ##STR4##

DETD . . . to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, **bromfenac**, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456,. . .

DETD . . . agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted **ophthalmic**, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount is referred to herein. . .

DETD The compositions are typically administered to the affected **ophthalmic**, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable. . . four times per day. However, the compositions may also be formulated as irrigating solutions that are applied to the affected **ophthalmic**, otic or nasal tissues during surgical procedures.

DETD The **ophthalmic**, otic and nasal compositions of the present invention will contain one or more compounds of formula (I) and preferably one. . . agents, in pharmaceutically acceptable vehicles. The compositions will typically have a pH in the range of 4.5 to 8.0. The **ophthalmic** compositions must also be formulated to have osmotic values that are compatible with the aqueous humor of the eye and **ophthalmic** tissues. Such osmotic values will generally be in the range of from about 200 to about 400 milliosmoles per kilogram. . .

DETD **Ophthalmic**, otic and nasal pharmaceutical products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during. . .

DETD The following examples are provided to further illustrate the **ophthalmic**, otic and nasal compositions of the present invention.

DETD

**Ophthalmic**/Otic/Nasal Solution

| Ingredient | Amount (wt. %) |
|---|---|
| Moxifloxacin | 0.35 |
| Sodium Acetate | 0.03 |
| Acetic Acid | 0.04 |
| Mannitol | 4.60 |
| EDTA | 0.05 |
| Benzalkonium Chloride. . . | |

DETD

**Ophthalmic**/Otic/Nasal Suspension

Ingredient Amount (wt. %)

Moxifloxacin 0.3
Dexamethasone, Micronized USP 0.10
Benzalkonium Chloride 0.01
Edetate Disodium, USP 0.01
Sodium Chloride, USP 0.3
Sodium Sulfate, USP 1.2
**Tyloxapol**, USP 0.05
Hydroxyethylcellulose 0.25
Sulfuric Acid and/or q.s. for pH adjustment to 5.5
Sodium Hydroxide, NF
Purified Water, USP q.s. to 100
DETD

**Ophthalmic** Ointment
Ingredient Amount (wt. %)

Moxifloxacin 0.35
Mineral Oil, USP 2.0
White petrolatium, USP q.s 100
DETD

**Ophthalmic** Ointment
Ingredient Amount (wt. %)

Moxifloxacin 0.3
Fluorometholone Acetate, USP 0.1
Chlorobutanol, Anhydrous, NF 0.5
Mineral Oil, USP 5
. . .
CLM What is claimed is:
1. A topical pharmaceutical composition for treating acute otitis externa infections or **ophthalmic** infections attributable to a Microbacterium species selected from the group consisting of Microbacterium otitidis and Microbacterium alconae, comprising of one.
. .
CLM What is claimed is:
6. A method of treating acute otitis externa infections or **ophthalmic** infections attributable to a Microbacterium species selected from the group consisting of Microbacterium otitidis and Microbacterium alconae, which comprises instilling. . .
IT Drug delivery systems
(**ophthalmic**; antibiotic compns. for treatment of eye and ear and nose disorders)

L9 ANSWER 38 OF 38 USPAT2 on STN
ACCESSION NUMBER: 2002:48047 USPAT2
TITLE: Use of a celecoxib composition for fast pain relief
INVENTOR(S): Karim, Aziz, Skokie, IL, United States
Brugger, Andrew M., Libertyville, IL, United States
Gao, Ping, Portage, MI, United States
Hassan, Fred, Peapack, NJ, United States
Forbes, James C., Glenview, IL, United States

PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6579895 | B2 | 20030617 | <-- |
| APPLICATION INFO.: | US 2001-866165 | | 20010525 (9) | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-207729P | 20000526 (60) |
| DOCUMENT TYPE: | Utility | |
| FILE SEGMENT: | GRANTED | |
| PRIMARY EXAMINER: | Cook, Rebecca | |
| LEGAL REPRESENTATIVE: | Harness, Dickey & Pierce | |
| NUMBER OF CLAIMS: | 29 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 4 Drawing Figure(s); 4 Drawing Page(s) | |
| LINE COUNT: | 1140 | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of ICI), propylene glycol laurate (e.g., Lauroglycol.TM. of Gattefosse), sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, **tyloxapol**, and mixtures thereof. Presently preferred examples include polysorbate 80 and sodium lauryl sulfate.

DETD . . . conditions such as psoriasis, eczema, acne, bums, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following **ophthalmic** surgery such as cataract surgery or refractive surgery.

DETD Such compositions are useful in treatment of **ophthalmic** diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

DETD . . . ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, **bromfenac**, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen,. . .

=> FIL STNGUIDE

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 136.82 | 147.72 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -1.70 | -1.70 |

FILE 'STNGUIDE' ENTERED AT 16:28:53 ON 14 JUN 2010
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT

10/525006



FILE CONTAINS CURRENT INFORMATION.
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